

Claims:

1. A method of detecting myocardial ischemia in a human or non-human body, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body whereby to identify regions of abnormal blood flow.
2. A method as claimed in claim 1 wherein said magnetic resonance imaging procedure is one capable of generating images with time intervals of less than 100 milliseconds.
3. A method as claimed in claim 1 or claim 2 wherein said imaging procedure is a gradient echo or echo planar imaging procedure.
4. A method as claimed in claim 3 wherein said imaging procedure is an inversion recovery echo planar imaging procedure.
5. A method as claimed in claim 3 or claim 4 wherein said imaging procedure is one in which TI (inversion time) is 100 to 800 msecs, TR (repetition time) is 2000 msecs and TE (echo time) is less than 20 msecs.
6. A method as claimed in any preceding claim wherein said manganese complex or salt thereof is administered at a dosage of 0.005 to 0.2 mmol/kg bodyweight.
7. A method as claimed in claim 6 wherein said manganese complex or salt thereof is administered at a dosage of 0.01 to 0.05 mmol/kg bodyweight.

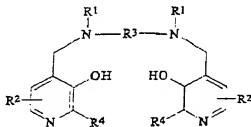
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8. A method as claimed in any preceding claim wherein said manganese complex is a manganese chelate complex having a  $K_a$  value of from  $10^7$  to  $10^{25}$ .

9. A method as claimed in claim 8 wherein said chelate has a  $K_a$  in the range of from  $10^{12}$  to  $10^{22}$ .

10. A method as claimed in claim 8 or claim 9 wherein said chelate has a  $K_a$  value smaller by a factor of at least  $10^3$  than the  $K_a$  value of the corresponding ferric ( $Fe^{3+}$ ) chelate.

11. A method as claimed in any one of claims 8 to 10 wherein said manganese chelate comprises a chelating compound of formula I:



(I)

or a salt thereof

(wherein in formula I

each R<sup>1</sup> independently represents hydrogen or -CH<sub>2</sub>COR<sup>5</sup>;

R<sup>3</sup> represents hydroxy, optionally hydroxylated alkoxy, amino or alkylamido;

each R<sup>2</sup> independently represents a group XYR<sup>6</sup>;

X represents a bond, or a C<sub>1-3</sub> alkylene or oxoalkylene group optionally substituted by a group R<sup>7</sup>;

Y represents a bond, an oxygen atom or a group NR<sup>6</sup>;

R<sup>6</sup> is a hydrogen atom, a group COOR<sup>5</sup>, an alkyl, alkenyl, cycloalkyl, aryl or aralkyl group optionally substituted by one or more groups selected from COOR<sup>5</sup>, CONR<sup>8</sup>, NR<sup>8</sup>, OR<sup>8</sup>, =NR<sup>8</sup>, =O, OP(O)(OR<sup>6</sup>)R<sup>7</sup> and OSO<sub>2</sub>M;

R<sup>7</sup> is hydroxy, an optionally hydroxylated, optionally alkoxyated alkyl or aminoalkyl group;

R<sup>8</sup> is a hydrogen atom or an optionally hydroxylated, optionally alkoxyated alkyl group;

M is a hydrogen atom or one equivalent of a physiologically tolerable cation;

R<sup>3</sup> represents a C<sub>1-8</sub> alkylene group, a 1,2-cycloalkylene group, or a 1,2-arylene group; and

each R<sup>4</sup> independently represents hydrogen or C<sub>1-3</sub> alkyl).

12. A method as claimed in claim 11 wherein in formula I:

R<sup>5</sup> is hydroxy, C<sub>1-8</sub> alkoxy, ethylene glycol, glycerol, amino or C<sub>1-8</sub> alkylamido;

X is a bond or a group selected from CH<sub>2</sub>, (CH<sub>2</sub>)<sub>2</sub>, CO, CH<sub>2</sub>CO, CH<sub>2</sub>CH<sub>2</sub>CO or CH<sub>2</sub>COCH<sub>2</sub>;

Y is a bond;

R<sup>6</sup> is a mono- or poly(hydroxy or alkoxyated) alkyl group or a group of the formula OP(O)(OR<sup>8</sup>)R<sup>7</sup>; and

R<sup>7</sup> is hydroxy or an unsubstituted alkyl or aminoalkyl group.

13. A method as claimed in claim 11 or claim 12 wherein in formula I, R<sup>3</sup> is ethylene and each group R<sup>4</sup> represents -CH<sub>2</sub>COR<sup>5</sup> in which R<sup>5</sup> is hydroxy.

14. A method as claimed in any one of claims 11 to 13 in which the compound of formula I is N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid (DPDP) or N,N'-dipyridoxyl-ethylenediamine-N,N'-diacetic acid (PLED).

15. A method as claimed in any one of claims 8 to 10 wherein said chelate complex is a complex of a linear, branched or macrocyclic chelant selected from polyaminopolycarboxylic acid chelants and carboxylic acid derivatives thereof.

16. A method of detecting myocardial ischemia in a human or non-human body, said method comprising administering to said body a physiologically acceptable manganese chelate complex, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body whereby to identify regions of abnormal blood flow, wherein said complex has a  $K_1$  value of from  $10^7$  to  $10^{25}$  and is a complex of a chelant selected from the group consisting of N,N,N',N',N"-diethylenetriaminepentaacetic acid (DTPA) and 6-carboxymethyl-3,9-bis(methylcarbamoyl-methyl)-3,6,9-triazaundecanedioic acid (DTPA-BMA).

17. A method of evaluating the severity of myocardial ischemia in a human or non-human body, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure as defined in any one of claims 1 to 5 and thereafter providing a series of images of the myocardium of said body whereby to indicate the degree of blood perfusion deficit in the myocardium.

18. A method of monitoring reperfusion of the myocardium of a human or non-human body, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure as defined in any one of claims 1 to 5 and thereafter providing a series of images of the myocardium of said body whereby to identify regions of reperfusion.

19. A method of discriminating between reversibly and irreversibly injured myocardial tissue, said method

comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure as defined in any one of claims 1 to 5 and thereafter providing a series of images of the myocardium of said body whereby to discriminate reversibly from irreversibly injured tissue.

20. A method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, within a period of from 3 to 6 hours following administration of said complex or salt thereof subjecting said body to a magnetic resonance imaging procedure as defined in any one of claims 1 to 5 and thereafter providing a series of images of the myocardium of said body whereby to distinguish viable myocardial tissue from infarcted tissue.

21. Use of a physiologically acceptable manganese complex or salt thereof for the manufacture of a contrast medium for use in a method as claimed in any one of claims 1 to 20.

22. A method of detecting myocardial ischemia in a human or non-human body, said method comprising administering to said body a physiologically acceptable chelate complex of a manganese radionuclide, or a salt thereof, detecting radiation emitted from the myocardium of said body and generating images of said myocardium whereby to identify regions of abnormal blood flow therein.

23. A method of evaluating the severity of myocardial ischemia in a human or non-human body, said method comprising administering to said body a physiologically

acceptable chelate complex of a manganese radionuclide, or a salt thereof, detecting radiation emitted from the myocardium and generating an image or images of the myocardium of said body whereby to indicate the degree of blood perfusion deficit in the myocardium.

24. A method of discriminating between reversibly and irreversibly injured myocardial tissue in a human or non-human body, said method comprising administering to said body a physiologically acceptable chelate complex of a manganese radionuclide, or a salt thereof, detecting radiation emitted from the myocardium and generating an image or images of the myocardium of said body whereby to discriminate reversibly from irreversibly injured tissue.

25. A method of monitoring reperfusion of the myocardium of a human or non-human body, said method comprising administering to said body a physiologically acceptable chelate complex of a manganese radionuclide, or a salt thereof, detecting radiation emitted from the myocardium and generating an image or images of the myocardium of said body whereby to identify regions of reperfusion.

26. A method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue in a human or non-human body, said method comprising administering to said body a physiologically acceptable chelate complex of a manganese radionuclide, or a salt thereof, detecting radiation emitted from the myocardium and generating an image or images of the myocardium of said body whereby to distinguish viable myocardial tissue from infarcted tissue.

27. A method as claimed in any one of claims 22 to 26 wherein said images are generated within a period of up to about 4 hours following administration of said

chelate complex or salt thereof.

28. A method as claimed in any one of claims 22 to 27 wherein said manganese radionuclide is  $^{51}\text{Mn}$ ,  $^{52}\text{Mn}$ ,  $^{52\text{m}}\text{Mn}$  or  $^{54}\text{Mn}$ .

29. A method as claimed in claim 28 wherein said radionuclide is complexed by a chelating compound as defined in any one of claims 11 to 16.

30. Use of a physiologically acceptable manganese complex or salt thereof for the manufacture of a contrast medium for use in a method of diagnosis involving image generation using a method as claimed in any one of claims 22 to 29.